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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,060	02/12/2002	David Mu	38002-0024	2406

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/073,060	MU ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,9,11,22,24,39,40,42,52,58-64,67-70,73,74 and 77-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,9,11,22,24,39,40,42,52,58-64,67-70,73,74 and 77-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on May 27, 2008 has been entered.

Claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 52, 58-64, 67-70, 73, 74 and 77-82 are pending in the instant application.

Claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 52, 58-64, 67-70, 73, 74 and 77-82 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Applicant's Amendment and Response filed May 27, 2008 have been considered. Rejections and/or objections not reiterated from the previous Office Action mailed February 25, 2008 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Response to Amendment

It is noted that in their request for continued examination filed May 27, 2008, Applicants have submitted Appendix 1, Appendix 2, and Appendix 3. Each of these appendices has been fully considered by the Examiner as acknowledged below.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed February 25, 2008, claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 52, and 58-64 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed February 25, 2008.

Response to Arguments

In response to this rejection, Applicants acknowledge that the specification at page 21, lines 12-19 discloses:

> The term "hepsin" refers to hepsin nucleic acid (DNA and RNA), protein (or polypeptide), and can include their polymorphic variants, alleles, mutants, and interspecies homologs that have (i) substantial nucleotide sequence homology with the nucleotide sequence of the GenBank entry M18930 (human hepsin mRNA, complete cds); or (ii) at least 65% sequence homology with the amino acid sequence of the SWISS-PROT record P05981 (serine protease hepsin); or (iii) substantial nucleotide sequence homology with the nucleotide sequence as set forth in SEQ ID NO: 1; or (iv) substantial sequence homology with the encoded amino acid sequence.

However, Applicants argue that the specification plainly states that the term "hepsin" can (i.e. does not necessarily) include the criteria set forth in items (i) through (iv).

This argument has been fully considered, but is not found persuasive because

Applicant is reminded that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. Thus, interpreted broadly, the term "hepsin" does necessarily include the criteria set forth in items (i) through (iv) above.

Applicants next argue that using human coding sequences as examples, sequences encoding hepsin family members do not have “substantial nucleotide sequence homology with the nucleotide sequence of GenBank entry M18930” as required by item (i) or with SEQ ID NO:1 as required by item (iii) above. Applicants point the Examiner to Appendix 1 and Appendix 2 filed May 27, 2008. Applicants contend that the only sequences which have a significant similarity with GenBank entry M18930 are hepsin sequences as detailed in Applicant's Appendix 3 filed May 27, 2008.

This argument and contention have been fully considered, but are not found persuasive. First, the Examiner acknowledges the information provided in Applicant’s Appendix 1, Appendix 2, and Appendix 3 filed May 27, 2008.

Second, Regarding Applicant’s Appendix 1, which Applicants contend demonstrates “no significant similarity” between hepsin and hepsin family members, it is unclear how this Blast search derived at such a conclusion. For example, it is unclear that, according to the Blast search, what would be considered "significantly similar"? While the search parameters of the Blast search are clearly defined and outlined, it is not clear what value these parameters are based against. Therefore, it cannot be said that the search parameters used in the Blast search would return hits or sequences that have “substantial nucleotide sequence homology with the nucleotide sequence of

GenBank entry M18930" as required by item (i) or with SEQ ID NO:1 as required by item (iii) above. Furthermore, regarding the specific phrase "substantial nucleotide sequence homology" it should be noted that Applicant's specification, at page 20, lines 6-11 discloses:

> The term "substantial identity" or "homologous" in their various grammatical forms means that a polynucleotide comprises a sequence that has a desired identity, for example, at least 60% identity, preferably at least 70% sequence identity, more preferably at least 80%, still more preferably at least 90% and most preferably at least 95%, compared to a reference sequence using one of the alignment programs described using standard parameters.

Thus, given this explicit definition, it is clear that the polymorphic variants, alleles, mutants, and interspecies homologs of hepsin as detailed in Applicant's claimed invention have "substantial nucleotide sequence homology with the nucleotide sequence of the GenBank entry M18930 (human hepsin mRNA, complete cds)", meaning have "a desired identity" with the nucleotide sequence of the GenBank entry M18930 (human hepsin mRNA, complete cds. Given the fact that the Blast search provided in Appendix 1 is not explicit in what is considered "significantly similar", and does not define the basis for the search parameters, it cannot be said that such a Blast search would even return hits that meet the criteria set forth in Applicant's disclosure.

Applicants next argue that using human proteins as examples, none of the hepsin subfamily members identified in Applicant's Appendix 1 has "at least 65% sequence homology with the amino acid sequence of SWISS-PROT record P05981" (human hepsin) as required by item (ii) or with the amino acid encoded by SEQ ID NO:1 (identical to GenBank entry M18930) as required by item (iv) above.

This argument and contention have been fully considered, but are not found persuasive because it should be noted that based on Applicant's definition of the term "substantial identity" at page 20, lines 26-31, the hepsin subfamily members need only have “a desired identity” with the amino acid sequence of SWISS-PROT record P05981 (human hepsin) or with the amino acid encoded by SEQ ID NO:1 (identical to GenBank entry M18930) and not have at least **65%** sequence homology with the amino acid sequence of SWISS-PROT record P05981 (human hepsin) as required by item (ii) or with the amino acid encoded by SEQ ID NO:1 (identical to GenBank entry M18930) as required by item (iv) above as Applicants contend. Thus, given Applicant's disclosure, "a desired identity" can be any real number. It is noted that the definition also recites, “at least 60%”, “at least 70%”, “at least 80%”, “at least 90%”, and “at least 95%”, however these are preferred embodiments and are not necessarily requirements of the claims.

Applicants next argue that there is no evidence to support the Examiner’s broad construction of the term “hepsin gene”.

This argument has been fully considered, but is not found persuasive because as discussed *supra*, the specification at page 21, lines 12-19 discloses:

> The term "hepsin" refers to hepsin nucleic acid (DNA and RNA), protein (or polypeptide), and can include their polymorphic variants, alleles, mutants, and interspecies homologs that have (i) substantial nucleotide sequence homology with the nucleotide sequence of the GenBank entry M18930 (human hepsin mRNA, complete cds); or (ii) at least 65% sequence homology with the amino acid sequence of the SWISS-PROT record P05981 (serine protease hepsin); or (iii) substantial nucleotide sequence homology with the nucleotide sequence as set forth in SEQ ID NO: 1; or (iv) substantial sequence homology with the encoded amino acid sequence.

The specification also discloses at page 20, lines 6-11:

> The term "substantial identity" or "homologous" in their various grammatical forms means that a polynucleotide comprises a sequence that has a desired identity, for example, at least 60% identity, preferably at least 70% sequence identity, more preferably at least 80%, still more preferably at least 90% and most preferably at least 95%, compared to a reference sequence using one of the alignment programs described using standard parameters.

Given Applicant's definition of "hepsin" and "substantial identity", the claims include hepsin and polymorphic variants, alleles, mutants and interspecies homologs that have "a desired identity" with the nucleotide sequence of the GenBank entry M18930, or "a desired identity" with SEQ ID NO:1, or "a desired identity" with the encoded amino acid sequence encoded by SEQ ID NO:1. Thus, given Applicant's disclosure, "a desired identity" can be any real number. It should be noted that while the definition also recites, "at least 60%", "at least 70%", "at least 80%", "at least 90%", and "at least 95%", it should be noted that these are preferred embodiments and are not necessarily requirements of the claims. Therefore, given Applicant's explicit teachings and disclosures, it is quite evident how the Examiner is supporting the broad construction of the term "hepsin".

It should also be noted that it appears that Applicant is neglecting another main issue of the instant rejection. Another main issue of the rejection, as paraphrased in the previous Office Action mailed September 7, 2007, at page 7, is that the specification does not describe the genus of the hepsin genes (as defined in Applicant's specification) that satisfies either the Lilly or Enzo standards. There are insufficient structural features common to all members of the genus of hepsin subfamily members.

This fact is evidenced and detailed in Applicant's Appendix 2, filed May 27, 2008, at pages 2 and 3, which details dozens of GenBank sequences having significant alignment to human hepsin (GenBank entry M18930). The only hepsin subfamily member specifically described in the specification associated with cancer or tumor samples is the hepsin gene identified by SEQ ID NO:1 (identical to GenBank entry M18930). One singly disclosed species of hepsin subfamily does not sufficiently describe the large and broad genus of the hepsin subfamily and does not meet the standard set forth in Lilly. Particularly when Applicants have defined "hepsin" to include polymorphic variants, alleles, mutants and interspecies homologs that have "a desired identity" with the nucleotide sequence of the GenBank entry M18930, or "a desired identity" with SEQ ID NO:1 of Applicant's invention. Additionally, the specification does not describe sufficient structural characteristics that correlate with the ability of the genus of the hepsin subfamily to function as contemplated by the specification and for the reasons set forth above do not meet the standards set forth by Enzo.

Therefore, based on the broad definition of the term "hepsin" (e.g. nucleic acid sequences that have substantial nucleotide sequence homology with the nucleotide sequence of the GenBank entry M18930, where "substantial identity" has been defined by Applicant to be "a desired identity"), the large genus of hepsin genes recited in the instant claims encompasses structurally and functionally distinct molecules, which have not been taught or described in the specification, whose amplification would not necessarily be expected to be associated with cancer, breast, lung, ovarian, prostate, or otherwise.

Thus, the specification does not provide an adequate written description of the genus of the hepsin gene subfamily in claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 52, and 58-64 that is required to practice the claimed invention.

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In the previous Office Action mailed February 25, 2008, claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 52, 58-64, 67-70, 73, 74 and 77-82 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed February 25, 2008.

Response to Arguments

In response to this rejection, Applicants argue that, contrary to the Examiner's assertions, the specification does explicitly teach analysis of control tissue. For example, Applicants point the Examiner to pages 42 and 64.

This argument has been fully considered, but is not found persuasive because while Applicant's specification generally and prophetically teaches comparison to appropriate controls (see page 42 and 62, for example), such an analysis was not demonstrated, particularly when the claims are drawn to specific levels of amplification (e.g. decrease or increase, 2.5 fold or 5 fold). Without a proper comparison to a control, the data presented is void of any values proving statistical significance and provides no explanations as to how much amplification is seen as significant in comparison to a

control. As discussed in the previous Office Action dated September 7, 2007, Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. For example, Thisted taught that it has become scientific convention to say that a P-value of 0.05 is considered significant (see page 5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion. Thus, absent comparison to a control tissue sample, it cannot be said that the data presented in Applicant's disclosure indeed indicates that detection of hepsin gene amplification (increase or decrease) provides for reliable and functional methods as claimed in Applicant's invention.

Applicants next argue that the specification need not teach, and preferably omit, what is well known in the art. Applicants contend that use of a proper control is not something which needs to be described in detail to enable the claimed methods. Applicants point the Examiner to M.P.E.P. § 2164.04.

This argument and contention have been fully considered, but not found persuasive. First, the issue is not that the specification teaches or does not teach what is well known in the art. The Examiner acknowledges that the art is well-set regarding methods of screening or methods of monitoring using proper and appropriate controls. This issue is, however, that Applicant's claims require the detection of hepsin gene amplification (increase or decrease), where the data lacks proper controls. As discussed *supra*, without a proper comparison to a control, the data presented is void of any values proving statistical significance and provides no explanations as to how much

amplification is seen as significant in comparison to a control. This is particularly evident at Table 2 of Applicant's disclosure where hepsin copy number for normal human tissue is "not determined". Further, Table 4 discloses the amplification of the hepsin gene in ovarian, lung, breast, and prostate tumors, without any analysis of respective non-tumor tissue.

Second, contrary to Applicant's assertions, the use of a proper control is something which needs to be described in detail to enable the claimed methods, particularly when the methods are of an unpredictable nature. As discussed in the previous Office Action mailed September 7, 2007, the prior art teaches much unpredictability regarding the role of hepsin in biological processes and gene association studies in general. For example, Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong. Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding. Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods [emphasis added], should be included in the gene association studies.

Wu et al. teach, "The physiological function of hepsin remains unknown" (see Abstract). The paper goes on to teach that, "In renal cell carcinomas, Zacharaski et al. reported strong hepsin staining on tumor cell membrane in all seven cases examined… However, two groups reported different results". The paper also teaches, "Clearly, additional studies with more patient samples are needed to better understand hepsin

expression in renal cell carcinomas and its relationship with disease prognosis" (see page 5055, second column, first full paragraph). Additionally, the paper teaches, "The evidence of hepsin up-regulation in prostate cancer is striking but the biological significance remains unclear" (see page 5055, second column, second full paragraph). As such, the state of the art provides unpredictability regarding the reliable practice of gene-association studies and specifically the hepsin gene.

This unpredictability is maintained with the lack of data regarding hepsin gene amplification in any non-tumor samples. For example, as discussed in the previous Office Action mailed September 7, 2007, Kandel et al (2001) teaches an analysis of amplification of the cyclin D1 gene amplification in breast cancer. The reference teaches that, taking into account the lack of amplification in some cases, and the presence of amplification in some controls (see Table 2), there is not a significant association between gene amplification and risk of breast cancer (p.43 – Abstract; p.49 – left col., lns.16-18). Based on the above, it is thus unpredictable as to how one might use methods determining any level of hepsin gene amplification increase, decrease or otherwise, without an appropriate and proper control.

Taking into consideration the factors outlined above, coupled with the known unpredictability in the art, the *Wands factors* have been weighed and favor undue experimentation. Based on the evidence of record, it is concluded that the specification fails to teach how to make and use the claimed invention without undue experimentation.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James "Doug" Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

July 30, 2008
/Terra Cotta Gibbs/

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/073,060	MU ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	